Studies on pharmacokinetics and metabolism of ferulic acid

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Abstract
Ferulic acid (FA) is presented in many Chinese traditional medicines, such as Ferula assafoetida L., Angelica sinensis (Oliv.) Diels, Ligusticum chuanxiong Hort., Lycopodium selago L., Equisetum hiemale L., Cimicifuga foetida L., Oryza sativa L., Allium cepa L., Rapharns sativus L., Catalpa ovata G. Don, Anthemis nobilis L. and Bougainvillea glabra Choisy. FA has lots of biological responses and pharmacological activities. It exhibits a wide range of therapeutical effects against various diseases like cancer, diabetes, cardiovascular and neurodegenerative. So there has been considerable public and scientific interest in the use of phytochemicals derived from dietary components to combat human diseases. In order to understand the study and applications of FA, We summarized the recent advances. This review includes the FA of bioanalysis method studies, metabolism and transportation mechanism, preclinical pharmacokinetics, and clinical pharmacokinetics.

Key words Ferulic acid; metabolism; pharmacokinetics; transportation; animals; patients

Introduction
Phenolic acids, which as dihydrocaffeic acid, dihydroferulic acid, caffeic acid, ferulic acid, and isoferulic acid (Fig 1), are found not only in food but also in traditional herbal Chinese medicines and supplements. The foods containing phenolic acids are fruits, vegetables, beverage, and cereals. Ferulic acid [FA, chemical name is 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid, or 4-hydroxy-3-methoxycinnamic acid] is presented in many Chinese traditional medicines, such as Ferula assafoetida L., Angelica sinensis (Oliv.) Diels, Ligusticum chuanxiong Hort., Lycopodium selago L., Equisetum hiemale L., Cimicifuga foetida L., Oryza sativa L., Allium cepa L., Rapharns sativus L., Catalpa ovata G. Don, Anthemis nobilis L. and Bougainvillea glabra Choisy.[1,2] FA has wide biological effects related to their antioxidant, anti-inflammatory, antitumor activities. FA protected against some chronic diseases such as diabetes[3], Alzheimer’s disease, and colon and breast cancers[4]. FA has been also shown to potentially exert several beneficial effects on health. However, the in vivo activity of ferulic acid strongly depends on its absorption, further metabolism, and tissue distribution. This review paper is to introduced the drug metabolism and pharmacokinetics of ferulic acid in vitro and in vivo in animals or humans.
Bioanalysis method studies

A selective and sensitive reversed-phase high performance liquid chromatography method was developed and validated for the simultaneous determination of ferulic acid, danshensu, cryptotanshinone, and tanshinone IIA in rabbit plasma using p-hydroxybenzoic acid as internal standard. Liquid-liquid extraction was used for sample preparation. Liquid-liquid separation was successfully achieved on an Agilent HC-C18 column using a mobile phase composed of methanol-water (from 20:80 to 80:20, v/v) containing 0.5% (v/v) glacial acetic acid. The mobile phase was employing gradient elution at a flow rate of 1.0 ml/min. The method showed good linearity and no endogenous material interfered with the marked compounds and I.S. peaks. The limit of quantification of ferulic acid, danshensu, cryptotanshinone, and tanshinone IIA were 0.1, 0.03, 0.05, and 0.05 microg/ml, respectively. The average extract recoveries of the four compounds from rabbit plasma were all over 60%. The precisions determined from 5 days were all within 10%. The established method has been successfully applied in the pharmacokinetic study and drug interaction of ferulic acid, danshensu, cryptotanshinone, and tanshinone IIA in rabbits after intravenous administration of danxiongfang, a useful compound preparation of traditional Chinese medicine.\(^5\)

To study the pharmacokinetics and relative bioavailability of combination Radix Angelicae Sinensis and Cortex Cinnamomi. The content of ferulic acid in plasma was determined directly by HPLC after oral administration of Cortex Cinnamomi in combination individually with Radix Angelicae Sinensis. The plasma concentration-time curve were plotted. The main pharmacokinetic parameters and relative bioavailability were obtained. The plasma concentration-time curve of ferulic acid conformed to one-compartment model. The relative bioavailability of Cortex Cinnamomi combined with Radix Angelicae sinensis were 226.75%. By the statistical analysis, Cortex Cinnamomi combined with Radix Angelicae sinensis can increase the relative bioavailability of ferulic acid.\(^6\)

A study investigated biomarkers of the bioavailability and metabolism of hydroxycinnamate derivatives through the determination of the pharmacokinetics of their urinary elimination and identification of the metabolites excreted. Coffee was used as a rich source of caffeic acid derivatives and human supplementation was undertaken. The results show a highly significant increase in the excretion of ferulic acid, isoferulic acid, dihydroferulic acid, and vanillic acid postsupplementation relative to the levels presupplementation. Thus, ferulic acid, isoferulic acid, and dihydroferulic acid are specific biomarkers for the bioavailability and metabolism of dietary caffeic acid esters.\(^7\)

Topically-applied antioxidant drugs represent a successful strategy for protecting the skin against UV-mediated oxidative damage. However, the drugs can afford to the skin a satisfactory photoprotection only if able to permeate through the stratum corneum and thus to reach deeper cutaneous layers. Ferulic acids and caffeic, dissolved in saturated aqueous solutions at pH 3 or 7.2, have been tested for their capability to permeate through excised human skin mounted in Franz cells. At both pH values, ferulic and, at a lower degree, caffeic acids appeared able to permeate through the stratum corneum. The known higher lipophilicity of ferulic acid may explain the fact that it permeates through the stratum corneum better than caffeic acid. However, vehicle pH values proved to have no influence on biophenol skin permeation profile; this observed lack of pH effect may reflect the drug higher concentration attainable in saturated solutions at high pH. On the basis of the findings obtained in these in vitro experiments, we designed the schedule of a series of in vivo experiments, carried out to evaluate the ability of ferulic and caffeic acids to reduce, in healthy human volunteers, UVB-induced skin erythema, monitored by means of reflectance spectrophotometry. Ferulic and caffeic acids, dissolved in saturated aqueous solution pH 7.2, proved to afford a significant protection to the skin against UVB-induced erythema. To conclude, researchers have confirmed, by means of in vitro and in vivo experiments, that ferulic and caffeic acids may be successfully employed as topical...
protective agents against UV radiation-induced skin damage; however their skin absorption is not influenced by the pH of the formulation.[8]

Metabolism and transportation mechanism

The metabolism of ferulic acid has been investigated using solid-phase extraction and HPLC-DAD methods that were established to separate and analyze the metabolites in urine, feces and bile. Three metabolites, identified by enzymatic hydrolysis, HPLC-DAD, HPLC-MS and MS/MS, are all glucuronic acid conjugates of ferulic acid. Ferulic acid conjugated with one glucuronic acid at different positions produces M1 and M3. Ferulic acid conjugated with two glucuronic acids produces M2, which is the main metabolite.[9]

After oral administration of 5.28g and 1.06g of French maritime pine bark extract to a human volunteer, Ferulic acid and taxifolin, conjugated as glucuronide/sulphate, were excreted within 18h. The peak urinary excretion was observed approximately 2-3 h after intake. Recovery of ferulic acid in urine was 36-43% and 7-8% for taxifolin. Two further metabolites could be identified as delta-(3,4-dihydroxy-phenyl)-gamma-valerolactone and delta-(3-methoxy-4–hydroxyphenyl) -gamma-valerolactone conjugated with glucuronic acid/sulphate. These metabolites could also be detected after intake of 960 mg of a procyanidin fraction of French maritime pine bark extract. Both metabolites show maximal urinary excretion 8-12h after intake and are excreted within 28-34 h.[10]

The antioxidant dihydrocaffeic acid is a dietary constituent and a microbial metabolite of flavonoids. Orally administered to rats, dihydrocaffeic acid was very rapidly absorbed most probably by the gastric or duodenal epithelium and excreted in urine as free and conjugated forms. LC-MS2 analysis of plasma and urine samples allowed confident identification of the dihydrocaffeic acid metabolites. The parent compound was glucurononated, sulphated or methylated, on one of the hydroxyl groups present on its phenyl ring. All the dihydrocaffeic acid metabolites peaked in plasma within the first 30min following ingestion, suggesting a metabolism possibly by the gastric or duodenal cells and by the liver. Using *in vitro* and *ex vivo* models of the intestinal epithelium and the liver, the identity and source of the metabolites detected in vivo were examined. The data obtained suggest that, in rats, intestinal cells are more able to glucuronondate dihydrocaffeic acid, whereas liver favours sulphation. Moreover, glucurononation, sulphation and methylation seem to be regio-selective, preferably on the 3-OH of dihydrocaffeic acid. The methyl conjugate, dihydroferulic acid, was shown to be oxidized into ferulic acid by intestinal and hepatic cells, which were also able to perform the reverse reaction, the reduction of ferulic acid into dihydroferulic acid. As a conclusion, the main form of dihydrocaffeic acid circulating in plasma after its ingestion is a mixture of different primary and secondary metabolites.[11]

Hydroxycinnamic acids are antioxidant polyphenols common in the human diet, although their potential health benefits depend on their bioavailability. To study the hepatic uptake and metabolism, human hepatoma HepG2 cells were incubated for 2 and 18 h with caffeic, ferulic, and chlorogenic acids. Moderate uptake of caffeic and ferulic acids was observed versus a low absorption of chlorogenic acid, where esterification of the caffeic acid moiety markedly reduced its absorption. Methylation was the preferential pathway for caffeic acid metabolism, along with glucurononation and sulfation, while ferulic acid generated glucuronides as the only metabolites. Ferulic acid appeared to be more slowly taken up and metabolized by HepG2 cells than caffeic acid, with 73% and 64% of the free, nonmetabolized molecules detected in the culture medium after 18 h, respectively. In conclusion, hydroxycinnamic acids can be metabolized by the liver as suggested by the results obtained using HepG2 cells as a hepatic model system.[12]

Govoni et al investigated the *in vitro* metabolism of two (nitrooxy)butyl ester nitric oxide (NO) donor derivatives of flurbiprofen and ferulic acid, [1,1'-biphenyl]-4-acetic acid-2-fluoro-alpha-methyl-4-(nitrooxy)butyl ester (HCT 1026) and 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-(nitrooxy)butyl ester (NCX 2057), respectively, in rat blood plasma and liver subcellular fractions compared with (nitrooxy)butyl alcohol (NOBA) and glyceryl trinitrate (GTN). HCT 1026 and NCX 2057 undergo rapid ubiquitous carboxyl ester hydrolysis to their respective parent compounds and NOBA. The nitrate moiety of this latter is subsequently metabolized to inorganic nitrogen oxides (NOx), predominantly in liver cytosol by glutathione S-transferase (GST) and to a lesser extent in liver mitochondria. If, however, in liver cytosol, the carboxyl ester hydrolysis is prevented by an esterase inhibitor, the metabolism at the nitrate moiety level
does not occur. In blood plasma, HCT 1026 and NCX 2057 are not metabolized to NOx, whereas a slow but sustained NO generation in deoxygenated whole blood as detected by electron paramagnetic resonance indicates the involvement of erythrocytes in the bioactivation of these compounds. Differently from NOBA, GTN is also metabolized in blood plasma and more quickly metabolized by different GST isoforms in liver cytosol. The cytosolic GST-mediated denitration of these organic nitrates in liver limits their interaction with other intracellular compartments to possible generation of NO and/or their subsequent availability and bioactivation in the systemic circulation and extrahepatic tissues. We show the possibility of modulating the activity of hepatic cytosolic enzymes involved in the metabolism of (nitrooxy)butyl ester compounds, thus increasing the therapeutic potential of this class of compounds.[13]

Ferulic acid and p-coumaric acid are actively taken up by monocarboxylic acid transporter (MCT), whereas gallic acid, caffeic acid (CA), and rosmarinic acid (RA) are absorbed by paracellular diffusion in human intestinal Caco-2 cells, although CA has low affinity for MCT. We previously demonstrated that p-coumaric acid has a much higher absorption efficiency than gallic acid in rats, owing to the MCT-mediated absorption of p-coumaric acid in vivo. Here, absorption of orally administered CA and RA in rats has been studied to investigate their intestinal absorption characteristics and pharmacokinetics in vivo and to compare the results with those of p-coumaric and gallic acids obtained under identical conditions. Rats were given 100 micromol/kg body weight of CA and RA and blood was collected from the portal vein and abdominal artery after administration. CA, RA and their metabolites were quantified by a coulometric detection method using HPLC-ECD. The serum concentration of intact CA and RA in the portal vein peaked at 10 min after administration, with a Cmax of 11.24 micromol/L for CA and 1.36 µmol·L⁻¹ for RA. The AUC for intact CA and RA in the portal vein was calculated from the serum concentration-time profile to be 585.0 and 60.4 micromol min·L⁻¹, respectively. The absorption efficiency of CA was about 9.7-fold higher than that of RA. Overall, the absorption efficiency of these compounds in vivo increases in the order: gallic acid = RA < CA < p-coumaric acid, which is in good agreement with results obtained in Caco-2 cells in vitro.[14]

Ferulic acid was efficiently transported as the free form through an in vitro model for the colonic epithelium consisting of cocultured Caco-2 and mucusproducing HT29-MTX cells, with only a small amount transported as feruloyl-glucuronide or sulfate, together with some free dihydroferulic acid. This pattern of metabolism and permeation was also seen with the use of rat everted ascending and descending colon sacs. In the cell model, free ferulic acid permeated by passive diffusion, as judged by the linearity of the uptake over time and nonsaturable concentration dependence. The mechanisms of phenolic acid intake and their mammalian metabolism in the colon, where the mucus layer is the thickest. The in vitro model used was a coculture of enterocyte (Caco-2) and goblet-like (HT29-MTX) cells and was compared with rat everted ascending and descending colonic sacs; the sample analysis was performed by LC-MS, which allowed direct identification and quantification of both the free form and metabolites. To compare the in vitro model of Caco-2/HT29-MTX cocultures with colonic tissue, ferulic acid uptake and metabolism were studied using an ex vivo model of colonic epithelium consisting of everted sacs of ascending and descending colon. All the ferulic acid metabolites identified using the in vitro model were detected in the content of the everted sacs. Their identity was confirmed by multiple reactions monitoring (MRM), fragmenting the parent compounds and looking for pairs of daughter and parentions (Fig 2).[15]
The permeation was independent of tight junctions but strongly linked to the hydrophobicity of the different phenolic acids tested, suggesting a transcellular rather than a paracellular transport. Using inhibitors, we showed that only a small proportion (<20%) of the free ferulic acid transport was carrier-mediated. The production of metabolites in the basal chamber was lowered by 3-[3-[2-(7-chloroquinolin-2-yl)-vinyl][phenyl]-2-dimethylcarbonamylethylsulfanyl)methylsulfanyl]pro-pionic acid and increased by cyclosporin A, implying an involvement of multidrug resistance protein and P-glycoprotein transporters in the efflux of metabolites, respectively to the serosal and luminal sides. These results show that the form of ferulic acid available to the blood after passage across the colonic barrier would be mainly the free form, together with only a small percentage of conjugated and reduced ferulic acid.\(^{[15]}\)

**Preclinical pharmacokinetics**

To study pharmacokinetics of ferulic acid and paeoniflorin, a HPLC was used to determine ferulic acid and paeoniflorin concentration in serum at different times. 3P87 procedure was used to process concentration-time data after the mice were administered ig. Ferulic acid and paeoniflorin were detected from serum in the mice. The pharmacokinetics parameters were: Ferulic acid: Ke = 0.330±0.085 h\(^{-1}\), Ka = 0.555±0.133 h\(^{-1}\), t\(_{1/2(ka)}\) = 1.249±0.365 h, t\(_{1/2(ke)}\) = 2.101±0.665 h, T\(_{peak}\) = 2.062±0.396 h, C\(_{max}\) = 3.401±0.879 mg.L\(^{-1}\), AUC = 41.399±11.763 mg.h.L\(^{-1}\). Paeoniflorin: Ke = 0.511±0.117 h\(^{-1}\), Ka = 0.656±0.121 h\(^{-1}\), t\(_{1/2(ka)}\) = 1.056±0.263 h, t\(_{1/2(ke)}\) = 1.356±0.281 h, T\(_{peak}\) = 2.062±0.396 h, C\(_{max}\) = 3.401±0.879 mg.L\(^{-1}\), AUC = 16.047±3.767 mg.L\(^{-1}\). The present research provided valuable data for rational clinical practice of APRP.\(^{[16]}\)

Arginine - glycine - aspartic acid peptide (RGD) conjugation liposomes (RGD-liposomes) were evaluated for brain-targeting drug delivery. The flow cytometric in vitro study demonstrated that RGD-liposomes could bind to monocytes and neutrophils effectively. FA was loaded into liposomes. Rats were subjected to intrastriatal microinjections of 100 units of human recombinant IL-1beta to produce brain inflammation and caudal vein injection of three formulations (FA solution, FA liposome and RGD-coated FA liposome). Animals were sacrificed 15, 30, 60 and 120 min after administration to study the body distribution of the FA in the three formulations. HPLC was used to determine the concentration of FA in vivo with salicylic acid as internal standard. The results of body distribution indicated that RGD-coated liposomes could be mediated into the brain with a 6-fold FA concentration compared to FA solution and 3-fold in comparison to uncoated liposome. Brain targeted delivery was achieved and a reduction in dosage might be allowed.\(^{[19]}\)

Zhao et al Designed a model on the absorption-study for FA or FAA (a FA sugar ester) in rat stomach in situ.(Fig 3) which is modified one method of Barr and Riegelman. They determined the recovery of FA and its metabolites (FA sulfate/glucuronides) in rat gastric contents, gastric mucosa, portal vein plasma, celiac arterial plasma, bile, and urine after 2.25 micromol FA was administered in 0.5 mL physiological saline and incubated for 25 min in situ in the stomach of rats. Within 25 min, 74 ±11% of the administered FA disappeared from the stomach; later, FA was recovered in both free and conjugated forms in plasma, bile, and urine. On the other hand, only free FA was detected in the gastric contents and mucosa; it was also detected in the portal vein plasma as 49 ±5% of the total FA (all forms of FA). However, the
The absorption and metabolism in the small intestine of chlorogenic acid (5-O-caffeoylquinic acid), caffeic acid were studied in rats in order to determine whether chlorogenic acid is directly absorbed or hydrolysed in the small intestine. Chlorogenic and caffeic acids were perfused into a segment of ileum plus jejunum during 45 min (50 microm, 0.75 ml/min) using an in situ intestinal perfusion rat model with cannulation of the biliary duct, and were quantified together with their metabolites in perfusion effluent, bile and plasma. The net absorption (influent flux minus effluent flux) of phenolic acids and their metabolites accounted for 19.5% and 8% of the perfused caffeic and chlorogenic acids, respectively. A minor fraction of the perfused caffeic acid was metabolized in the intestinal wall and secreted back into the gut lumen in the form of ferulic acid (0.5 % of the perfused flux). Part of the chlorogenic acid (1.2 % of the perfused flux) was recovered in the gut effluent as caffeic acid, showing the presence of trace esterase activity in the gut mucosa. No chlorogenic acid was detected in either plasma or bile, and only low amounts of phenolic acids (less than 0.4 %) were secreted in the bile. The present results show that chlorogenic acid is absorbed and hydrolysed in the small intestine. In contrast to numerous flavonoids, absorbed phenolic acids are poorly excreted in the bile or gut lumen. Their bioavailability therefore appears to be governed largely by their uptake into the gut mucosa.[21]

Clinical pharmacokinetics

Chlorogenic acids (CGA) are cinnamic acid derivatives with biological effects mostly related to their antioxidant and antiinflammatory activities. Caffeoylquinic acids (CQA) and dicaffeoylquinic acids (diCQA) are the main CGA found in nature. Because green coffee is a major source of CGA, it has been used for production of nutraceuticals. However, data on the bioavailability of CGA from green coffee in humans are inexistent. The present study evaluated the pharmacokinetic profile and apparent bioavailability of CGA in plasma and urine of 10 healthy adults for 8 h after the consumption of a decaffeinated green coffee extract containing 170 mg of CGA. Three CQA, 3 diCQA, and caffeic acid, ferulic acid, isoferulic acid and p-coumaric acid were identified in plasma by HPLC-Diode Array Detector-MS after treatment. Over 30% (33.1±23.1%) of the ingested cinnamic acid moieties were recovered in plasma, including metabolites, with peak levels from 0.5 to 8 h after treatment. CGA and metabolites identified in urine after treatment were 4-CQA, 5-CQA, and sinapic, p-hydroxybenzoic, gallic, vanillic, dihydrocaffeic, caffeic, ferulic, isoferulic, and p-coumaric acids, totaling 5.5±10.6% urinary recovery of the ingested cinnamic and quinic acid moieties. This study shows that the major CGA compounds present in green coffee are highly absorbed and metabolized in humans.[22]
volunteers in a crossover study. Each subject received doses of both extracts. Extract A administered dose: caffeoylquinic acids equivalent to 107.0 mg caffeic acid and luteolin glycosides equivalent to 14.4 mg luteolin. Extract B administered dose: caffeoylquinic acids equivalent to 153.8 mg caffeic acid and luteolin glycosides equivalent to 35.2 mg luteolin. Urine and plasma analysis were performed by a validated HPLC method using 12-channel coulometric array detection. In human plasma or urine none of the genuine target extract constituents could be detected. However, caffeic acid (CA), its methylated derivatives FA and isoforcalic acid (IFA) and the hydrogenation products dihydrocaffeic acid (DHCA) and dihydroferulic acid (DHFA) were identified as metabolites derived from caffeoylquinic acids. Except of DHFA all of these compounds were present as sulfates or glucuronides. Peak plasma concentrations of total CA, FA and IFA were reached within 1 h and declined over 24 h showing almost biphasic profiles. In contrast maximum concentrations for total DHCA and DHFA were observed only after 6-7 h, indicating two different metabolic pathways for caffeoylquinic acids. Luteolin administered as glucoside was recovered from plasma and urine only as sulfate or glucuronide but neither in form of genuine glucosides nor as free luteolin. Peak plasma concentrations were reached rapidly within 0.5 h. The elimination showed a biphasic profile.[23]

To simultaneously determine the contents and explore the pharmacokinetics of ferulic acid and paeoniflorin by HPLC after oral administration of Modified Xiao-yao Decoction (MXYD), total of 8 healthy men were enlisted in this study. The serum samples were preprocessed by immersion method. The HPLC system was used to determine the contents of ferulic acid and paeoniflorin in the blood samples of the 8 healthy volunteers, and the blood was collected through the ulnar vein at 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 2 h and 3 h after MXYD administration. The dates of serum concentration-time were fitted by using the 3P97 analytical program of pharmacokinetics. The internal standard (IS) was coumarin. The detection wavelengths of paeoniflorin and ferulic acid were 230 nm from 0 min to 10 min and 320 nm from 10 min to 25 min respectively. After MXYD administration, paeoniflorin and ferulic acid were separated completely in the serum and no other interfering peaks were found in the spectrum of the chromatograms. The retention times of the paeoniflorin and ferulic acid were 8.02 min and 13.32 min respectively, and that of the coumarin was 19.14 min. The calibration curve for paeoniflorin was linear over the concentration range 40-1 280 ng·mL⁻¹, Its low-detection limit based on a signal-to-noise ratio of 3 was 5 ng·mL⁻¹ and low-concentration limit was 15 ng·mL⁻¹ with RSD of 12.5%; FA was in the range 10-320 ng·mL⁻¹, its low-detection limit was 0.65 ng·mL⁻¹ and low-concentration limit was 5 ng·mL⁻¹ with RSD of 9.7%. The method was found to be highly precise, with RSD<5% and interday and intraday variability in the range of 92.1%-109.9% for each of the concentrations tested. This is a study on simultaneously determining paeoniflorin and ferulic acid in serum of healthy volunteers after oral administration of MXYD. The method is suitable for identifying the serum levels of ferulic acid in clinical investigations.[24]

Since plant extracts are increasingly used as phytotherapeutics or dietary supplements information on bioavailability, bioefficacy and safety are warranted. Eleven volunteers received a single dose of 300 mg pine bark extract, five volunteers ingested 200 mg daily for five days to reach steady state concentrations. Plasma samples were obtained before and at defined time points after intake of the extract. Samples were analyzed by HPLC with ion-pair reagents and simultaneous UV and electrochemical detection. Grimm et al quantified total plasma concentrations of ferulic acid, catechin, caffeic acid, taxifolin and the metabolite M1 (δ-(3,4-dihydroxy-phenyl)-γ-valerolactone). Additionally, It was described that plasma time courses and steady state appearance of ten so far unknown compounds. After single ingestion, compounds derived from the extract were rapidly absorbed and the majority of them were detectable over whole experimental period of 14 h.[25] Maximum plasma concentrations of ferulic acid were seen already after 0.5 to 1 h. Concentrations decreased thereafter and remained almost constant before revealing another increase towards the end of experimental period (Fig 4).

Ferulic acid has been previously described as a urine excretion marker of consumption of maritime pine bark extract[26] and thus it was expected to be present in plasma. Virgili et al observed an early tmax of 1 h for ferulic acid which is consistent with other reports of tmax values of 1-3 h[27] or 0.77 h[28] The tmax of about 15 nmol·L⁻¹ (≈75 nmol·L⁻¹) we observed after intake of the single dose Pycnogenol containing 975 µg free ferulic acid again appears to be high. After ingestion of 250 mg ferulic acid from breakfast cereals plasma concentrations of 150–210
nmol/L were described.[27]

The analysis of steady state plasma samples revealed significant phase II metabolism. The first systematic pharmacokinetic analysis of compounds derived from maritime pine bark extract. Beyond the known constituents and metabolites we uncovered the plasma time courses of ten unknown compounds. In concert with our previous detection of anti-inflammatory bioefficacy of these plasma samples ex vivo researchers suggest that constituents and metabolites of Pycnogenol bear potential for disclosure of novel active principles.[25]

Twenty-one healthy volunteers, 20 patients with syndrome of stagnation of liver qi and spleen deficiency, 22 patients with syndrome of deficiency of spleen qi and 19 patients with syndrome of excess of stomach heat were included and administered to take Jiawei Xiaoyaosan Recipe (JWXYSR). The serum PK parameters of FA were examined by a HPLC method. The distribution rate constant(α) and the elimination rate constant (β)were both decreased while the apparent first-order absorption constant(Ka) was enhanced significantly in the patients with syndrome of deficiency of spleen qi; the α, β and Ka were all reduced in the patients with syndrome of stagnation of liver qi and spleen deficiency; the β and Ka were increased in the patients with syndrome of excess of stomach heat, as compared with the corresponding PK parameters in the healthy volunteers. The PK analysis of FA in the patients with syndrome of deficiency of spleen qi shows that the absorption rate is accelerated, and both the distribution and elimination rates are slowed down. The absorption, distribution and elimination rates of FA are all slowed down in the patients with syndrome of stagnation of liver-qi and spleen deficiency, while the absorption and elimination rates of FA are both accelerated in the patients with syndrome of excess of stomach heat. There are obvious differences in the PK characteristics among these three syndromes.[29]

Conclusion

This review paper is indicates that the current studies on pharmacokinetics and metabolism of ferulic acid have acquired lots of efforts. FA has wide biological responses and pharmacological activities. According to reported literatures, the pharmacokinetics of FA has following characteristics: (1) Maximum plasma concentrations of ferulic acid absorbed by oral administration to rats were seen already after 0.5 to 1 h. The bioavailability of ferulic acid and its metabolites was investigated in rat plasma and urine after an oral short-term ingestion of FA. Free FA, glucuronoconjugates and sulfoconjugates were quickly detected in plasma with a peak of concentration found 30 min after ingestion. (2) The methyl conjugate, dihydroferulic acid, was shown to be oxidized into ferulic acid by intestinal and hepatic cells, which were also able to perform the reverse reaction, the reduction of ferulic acid into dihydroferulic acid. (3) The form of ferulic acid available to the blood after passage across the colonic barrier would be mainly the free form, together with only a small percentage of conjugated and reduced ferulic acid. (4) The absorption, distribution and elimination rates of FA are all slowed down in the patients with syndrome of stagnation of liver and spleen deficiency, while the absorption and elimination rates of FA are both accelerated in the patients with syndrome of excess of stomach heat. The potential of FA is large, and there still a great deal to do about it in the future.

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